Common genetic loci influencing plasma homocysteine concentrations and their effect on risk of coronary artery disease.

The strong observational association between total homocysteine (tHcy) concentrations and risk of coronary artery disease (CAD) and the null associations in the homocysteine-lowering trials have prompted the need to identify genetic variants associated with homocysteine concentrations and risk of CAD. We tested whether common genetic polymorphisms associated with
variation in tHcy are also associated with CAD. We conducted a meta-analysis of genome-wide association studies (GWAS) on tHcy concentrations in 44,147 individuals of European descent. Polymorphisms associated with tHcy (P < 10^(-8)) were tested for association with CAD in 31,400 cases and 92,927 controls. Common variants at 13 loci, explaining 5.9% of the variation in tHcy, were associated with tHcy concentrations, including 6 novel loci in or near MMACHC (2.1 × 10^-7), SLC17A3 (1.0 × 10^-7), GTPB10 (1.7 × 10^-7), CUBN (7.5 × 10^-8), HNF1A (1.2 × 10^-9), and FUT2 (6.6 × 10^-8), and variants previously reported at or near the MTHFR, MTR, CPS1, MUT, NOX4, DPEP1, and CBS genes. Individuals within the highest 10% of the genotype risk score (GRS) had 3-?mol/L higher mean tHcy concentrations than did those within the lowest 10% of the GRS (P = 1 × 10^-8). The GRS was not associated with risk of CAD (OR: 1.01; 95% CI: 0.98, 1.04; P = 0.49). We identified several novel loci that influence plasma tHcy concentrations. Overall, common genetic variants that influence plasma tHcy concentrations are not associated with risk of CAD in white populations, which further refutes the causal relevance of moderately elevated tHcy concentrations and tHcy-related pathways for CAD.